Dermatologic Therapeutics

- MTX
- Systemic retinoids
- Cyclosporine
- Biologics
- Phototherapy
- Sunscreens
- PDT
- Laser
- Antimalarials
- Dapsone
- Topical / Systemic Steroids

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Systemic treatments

General scheme

Chemistry (Structure)
Pharmacokinetics: ADME (significance??)

1. Absorption
2. Distribution / Bioavailability
3. Metabolism
4. Excretion

Pharmacodynamics:

1. Action(s)
2. Mechanism(s) of action

Pharmacotherapeutics:

1. Indications
    - FDA-approved
    - Off-label
2. Dosing
3. **Side effects مهم جدا ******
4. Contraindications
    - Absolute
    - Relative
5. Drug interactions
6. **Monitoring / Screening tests مهم جدا ******
    - **Baseline**
    - **Follow-up**
7. Remission / relapse

Side effects: اهمية
1- Contraindications
2- Monitoring (baseline / follow-up)
3- Drug interaction

Systemic treatment of psoriasis:
1. Methotrexate (MTX)
2. Acitretin (systemic retinoid)
3. Ciclosporin
4. Biologics
5. Phototherapy

Methotrexate (MTX)

Physiology:

Folic acid (folate) —(Folate reductase (FR))→ Dihydrofolate (DHF) —(FR)→ Tetrahydrofolate (THF) → DNA synthesis (S-phase) → Cell replication (Proliferation)

Chemistry: Folic acid **analogue**

Actions / Mechanism of action:

(1) Anti-proliferative:

Competitive irreversible <u>inhibition</u> of FR enzyme ⇨ inhibition of DNA synthesis ⇨ ↓ cell proliferation of

- **<u>KCs</u>** (e.g. treatment of psoriasis)
- **<u>T-cells</u>** (effect of MTX on the proliferation of lymphoid cells is 1000 times greater than its effect on KCs)

(2) Immunosuppressive:

- Inhibition of DNA synthesis in immunologically competent cells
- Blocks migration of activated T cells into tissues.

(3) Anti-inflammatory

Indications: ↓↓ *KCs proliferation + Immunosuppressive* الفكرة العامه

- **FDA-approved: <u>Psoriasis</u>** (erythrodermic, pustular, severe recalcitrant plaque)
- **↓↓ KCs proliferation:** PRP, PLEVA, PLC, lymphomatoid papulosis
- **Immunosuppressive (steroid-sparing):**
  - Immunobullous e.g. PV, BP
  - AI-CTDs e.g. SLE, DM, SSc
  - Vasculitis
  - Neutrophilic dermatoses e.g. Behcet's and PG
  - Sarcoidosis
- **Others: crusted (Norwegian) scabies** مهم جدا*****

NOTE: Steroid-sparing agents (2nd line treatment after steroids):
MTX, azathioprine, cyclophosphamide, IVIG, ciclosporin .....

Dosing:

15-25 mg / week + folic acid supplementation باختصار

Oral (2.5 mg tablets)	Parenteral (50 mg vial 1 ml/2 ml)
15 mg / week **Low-dose MTX** مهم	25 mg / week IM ½ الحقنه عضل كل اسبوع
Single dose OR **3 divided doses** within 12-hr interval i.e. 2 tablets (5 mg) x 3 times **[24 hrs]**	

Folic acid supplementation: 1-2 tablets daily **EXCEPT** day(s) of MTX

MTX aim is to ↓↓ folic acid. So, why to give folic acid?

(1) To prevent anemia (hematological side effect)

(2) To ↓↓ nausea and vomiting

BUT NOT given on day(s) of MTX? To avoid ↓↓ efficacy of MTX

Side effects (3x3)

Minor side effects: (3)

(1) Nausea and vomiting: commonest

- Patients may stop treatment because of it
- ***How to reduce??***
  - ☆ Folate supplementation
  - ☆ Parenteral (IM / IV) better than Oral
  - ☆ Divided doses (3 doses – 12 hrs interval)
  - ☆ Single dose at bed time

(2) Malaise & fatigue

(3) Stomatitis ***

Organ toxicity: (3)

(1) BM: myelosuppression (cytopenias)
megaloblastic anemia = earliest sign on CBC is ↑↑MCV

(2) Liver: hepatotoxicity (liver **fibrosis**)**********

(3) Lung: dyspnea, cough, pulmonary fibrosis

Others: (3)

(1) Immunosuppression: ↑↑ incidence of **infection**

(2) ♀ teratogenic, abortion
(pregnancy **category X – absolute contraindication**)

(3) ♂ **reversible oligozoospermia**
If male is on MTX and his partner is planning for pregnancy – when to get pregnant? Wait for **3 months** after stoppage of MTX

Side effect	Monitoring		Contra-indications
	Baseline	Follow-up	
BM	**CBC**	After 2 wks, monthly	Significant cytopenias
Liver	**LFTs** Liver biopsy (??)	Monthly	History/risk for liver disease
Lung	CXR (if symptoms)		History/risk for lung disease
Teratogenic	**Pregnancy test**	Monthly	Pregnancy (absolute)
Infection	CBC + tests for HIV / TB (tuberculin)		Any active / latent infection (TB)
Excretion	**Kidney FTs**		Renal disease
			Allergy, lactation

DO NOT FORGET: (3) side effects: BM + LIVER + Teratogenic & (3) tests: CBC + LFTs / renal + Pregnancy test

Test dose of MTX:

- Baseline CBC > 5mg (2 tablets) > repeat CBC after **1 week**
- To detect the rare BUT serious side effect of **severe myelosuppression (idiosyncracy)**

Liver biopsy:

Baseline:

زمان: لكل الحالات قبل بدء العلاج

دلوقتى: done **ONLY if risk factor** for liver diseases e.g.

- ☆ Abnormal (elevated) liver enzymes
- ☆ History of liver diseases e.g. HCV
- ☆ Family history of inherited liver disease e.g. Wilson's
- ☆ Hepatotoxic drugs
- ☆ Chemical exposures
- ☆ Alcohol, DM, Hyperlipidemia

Follow-up: (monitoring for fibrosis) **cumulative dose**

- ☆ If risk factor: **1 – 1.5** GRAMS
- ☆ If NO risk factor: **3.5 – 4** GRAMS

Alternatives to liver biopsy?? NON-invasive

- Serum assays for liver fibrosis:
  - Amino terminal peptide of pro-collagen III
  - Liver fibrosis kits
- Imaging: magnetic resonance elastography (MRE)

Drug interactions: مهم جدا

Drugs that ↑↑ liver toxicity of MTX:

- **Other anti-folates** (drugs that inhibit FR enzyme): synergistic / additional effect: **Sulfa drugs (TMP-SMX) e.g. septazole*****
- Other **hepatotoxic** drugs e.g. alcohol, systemic retinoids
- Drugs that ↓ **renal excretion** of MTX:
    - Probencides
    - Nephrotoxic drugs e.g. aminoglycosides, ciclosporin, NSAIDs

NOTES:

- **Metabolism** of MTX: **liver**
- **Excretion** of MTX: **renal**
- **Remission** (in psoriasis): 2-6 weeks **(time to respond)**
- **Relapse** (in psoriasis): 10 weeks – 6 months (**remission period after stoppage of MTX**)
- **Antidotes** of MTX (BM toxicity):
    - Folic acid
    - Folinic acid

Systemic retinoids

Chemistry: vitamin A derivatives

Mechanism of action:

- Cross plasma membrane (why??)
- Bind to cytosolic retinoic acid binding protein (**CRABP**) = cytoplasmic carrier
- Enter **nucleus** and bind to **nucleic receptors: 2 families:**
  - Retinoic acid receptors **(RARs): (α, β and γ)**
  - Retinoid X receptors **(RXRs): (α, β and γ)**
- Modify **gene** transcription and translation

Actions:

- Modulation of **KC proliferation and differentiation**
- Anti-acne and anti-**seborrheic** effects (↓ gland size / sebum production)
- **Immunologic** and **anti-inflammatory** effects
- **Tumor** prevention and therapy

Indications:

- **FDA-approved:**
  1. **Acitretin: psoriasis**
  2. **Isotretinoin: AV**
  3. **Bexarotene: MF**
- **Off-label: .....**

	Isotretinoin	**Acitretin**
	Isotretinoin, Netlook, Roaccutane 10, 20, 40 mg cap	Acitretin, Neotigasone 10, 25 mg cap
Main site of action	**Sebaceous gland** (↓ size and sebum production)	**KCs** (↓ KC proliferation)
	BUT there is OVERLAP ... تداخل بين الاثنين	
Indications	**FDA-approved: AV** ***Severe** (many lesions + impact on patient's QoL) ***Recalcitrant** (No response to other therapies e.g. systemic antibiotics) ***Nodulo-cystic**	**FDA-approved: psoriasis** ***Severe recalcitrant** plaque ***Pustular** ***Erythrodermic**

	Off-label: Rosacea Hidradenitis suppurativa Pyoderma faciale Dissecting cellulitis of the scalp	**Off-label:** Disorders of **keratinization** e.g. ichthyosis, Darier disease, Keratoderma Pityriasis rubra pilaris **Chemoprophylaxis** of neoplastic processes e.g. Xeroderma pigmentosum
	More with isotretinoin	**More with acitretin**
	BUT there is OVERLAP ... تداخل بين الاثنين	
Dose	**0.5 – 1 mg / kg / day** Total cumulative dose 120-150 mg/kg (4-5 months)	**0.5 – 1 mg / kg / day** (10-25 mg/day up to 50 mg/day) **NO** Total cumulative dose
	Initial flare (increased severity) in AV during first 4-5 weeks of treatment then improvement *How to deal: Patient education + Prednisolone 5 mg tab daily for 10 days*	**Initial flare (increased severity) in psoriasis**
Teratogenic	**In female patients, "contraception / avoid pregnancy" during and after stoppage. After stoppage, for how long?**	
	1 – 2 months	**2 – 3 years (up to 5)**
	T ½ = 10 – 20 hrs (ساعات)	**T ½ = 50 hrs (يومين)** ***Why 3 years?*** ** Etretinate (old drug) with T ½ = 80-160 days (5-6 months) ** Normal metabolism: etretinate → acitretin (the active metabolite of etretinate) ***** Reverse metabolism (Re-esterification): acitretin → etretinate (spontaneously OR with alcohol)***

NB: (the only systemic retinoid FDA-approved for AV is isotretinoin)
(the only systemic retinoid FDA-approved for psoriasis is acitretin)

Side effects: (ALL systemic retinoids)

(1) Teratogenicity: أول و أهم حاجه

- **Pregnancy category X (absolute contraindication)**
- Malformations (defects), spontaneous abortions, stillbirth
- Highest risk during **1st trimester** (BUT contraindicated throughout pregnancy)
- Higher risk with **isotretinoin > acitretin**
- ***Precaution during prescription for females during child-bearing period: Contraception***
    - 2 methods
    - At least 1 month before + during + after stoppage (1 month for isotretinoin, 3 years for acitretin)

(2) Hyperlipidaemia: تانى هام

- The **most common laboratory abnormality** with systemic retinoids
- **Risk factors:** alcoholic, obese, diabetic, sedentary life style
- **Reversible** (with stoppage of the drug)
- More with **TGs** > cholesterol
- Higher risk with **isotretinoin > acitretin**
- Drug can be used with hyperlipidemia (TGs) up to **double the base line of the patient العيان نفسه**
- ***How to manage hyperlipidemia?***
    - ☆ Mild (TGs 300-500 mg / dl): weight reduction, exercise, decrease (alcohol, fat, carbohydrate)
    - ☆ Moderate (TGs 500-800 mg / dl): dose reduction + statins
    - ☆ Mild (TGs 800-1000 mg / dl): STOP the drug (risk of pancreatitis)

(3) Muco-cutaneous: تالت هام

- Dryness (chelitis, dry nose = bleeding, dry eye = conjunctivitis, dry mouth, dry skin ≠ atopic patients)
    - Higher risk with **isotretinoin > acitretin**
    - **Dose-dependent**
- ↑ risk of infection
- ↓ thickness of stratum corneum
    - Photosensitivity
    - **Avoid use with laser, peeling,… risk of hypertrophic scar / keloid مهم**

(4) Neuro-psychiatric:

Higher risk with **isotretinoin / AV treatment**

- **Pseudo-tumor cerebri**
  - Benign ↑ in intracranial tension (ICT) = headache, nausea, vomiting, blurred vision…
  - **Isotretinoin combined with tetra-, doxy-, mino-cycline**
- **Depression, psychosis up to suicidal attempts**

(5) OTHERS:

- ☆ **Hepatotoxic: (MTX موش زی)**
  - Elevation of liver enzymes (mild – returns to normal even with continued treatment)
  - Severe or fatal hepatitis (rare – idiocyncracy – more with acitretin أول مره)
- ☆ **Musculo-skeletal:** myalgia, arthralgi, fatigue, muscle weakness
- ☆ **Bone:** periosteal bone formation, hperostosis, premature closure of epiphysis (children??)
- ☆ **Hair:** telogen effluvium (reversible, dose-dependent, more with **acitretin**)
- ☆ **Nail:** fragility, onycholysis, onychorrhexis
- ☆ **Blood:** cytopenias (very rare)

Side effect	Monitoring		Contra-indications
	Baseline	Follow-up	
Teratogenic	**Pregnancy test**	Monthly	**Pregnancy (absolute)** Likely to get pregnant Non-compliance with contraception
Hyper-lipidemia	Lipid profile (TG, C, HDL, LDL)	2 weeks, monthly, 3 months	**Hyperlipidemia** Caution with alcohol, DM, obese….
Liver	**LFTs**	Monthly	History/risk of liver disease (acitretin)
Bone	**X-ray spine, hands**		**Allergy, lactation**
Excretion	**Kidney FTs**		Renal disease
Blood	**CBC**		Cytopenias,

NOTES:

- All side effects (iso > aci) except liver + hair
- Serum lipid testing: fasting 10-12 hours

Drug interactions:

AVOID

- Alcohol and alcohol-containing products
  - Hyperlipidemia
  - Acitretin → etretinate
- Vitamin A → toxicity
- Tetracycline, doxycycline, minocycline

Cyclosporine-A

Sandimmune 25, 50, 100 mg cap

Mechanism of action:

- Systemic **Calcineurin inhibitor**
- **Cyclosporine** binds to the **cyclophilin** → complex → inhibits calcineurin → inhibits T-cell activation

Remember:
T-lymphocyte activation begins when epitopes complexed with MHC molecules on APCs interact with TCRs, together with CSM. This results in a cascade of events including:

- increase in the level of free **calcium (Ca^{2+})** within the cell.
- the calcium binds to **calmodulin.**
- calmodulin activates **calcineurin (phosphatase enzyme).**
- calcineurin dephosphorylates the cytoplasmic subunit of the nuclear factor of activated T cells **(NFATc-P).**
- The dephosphorylated subunit (NFATc) translocates to the nucleus → forms a complex with the nuclear subunit of the nuclear factor of activated T cells **(NFATn)** → transcription of numerous cytokines.

Action:

Immunosuppressant (steroid-sparing*)**

Indications:

- **FDA-approved:**
  - **Psoriasis** (pustular, erythrodermic, severe recalcitrant…)
  - **AD** (only in Europe)
- **Off-label: ((steroid-sparing – 2nd line after steroids)**
  - AI-Bullous e.g. PV, BP, LABD, EBA…
  - AI-CTDs e.g. LE, DM, Scleroderma…
  - Vasculitis: Behcet's, **pyoderma gangrenosum**, ….

Dose:

2.5 – 5 mg / kg / day (5 mg/kg/day is the maximum dermatologic dose)

◆**2 ways:** start at full dose **OR** start at a small dose then gradually increase (***0.5-1 mg /kg/day every 2 weeks***) till maximum dose is reached
◆If **NO RESPOSNE** on full dose after **3 months**, STOP the drug

Side effects:

(1) Nephrotoxicity:

- Depends on **dose** and **duration – Reversible**

(2) Hypertension:

- Depends on dose and duration – Reversible – mild
- **Due to** direct VC effect on renal arterioles smooth muscles + 2^{ry} to renal insufficiency
- Development of HTN is **not an indication to STOP the drug** as long as we can control it with anti-hypertensive drugs

(3) Malignancy: NMSC (mostly SCC), B- and T-cell **lymphomas**

(4) Hypertrichosis: the most common cutaneous side effect

(5) Gingival hyperplasia

(6) Others:

- **Hyper**lipidemia
- **Hyper**kalemia
- **Hyper**uricemia and gout
- ↓ ↓ **Mg** *****
- Neurologic: headache, tremors, paraesthesia
- GIT: nausea, vomiting, diarrhea, abdominal pain
- Musculoskeletal: arthralgia, myalgia, fatigue

كل حاجه تزيد ماعدا Mg

Monitoring:

- **Serum creatinine:** If increased > 25-30% baseline, decrease dose or stop drug, **Urine analysis, BUN, creatinine clearance**
- **ABP measurement and follow-up**
- **Lipid profile**
- **Serum electrolytes (K, Mg, Uric acid)**
- CBC
- LFTs

Contraindications:

- **Absolute: Renal dysfunction, HTN**, Malignancy (present / past history) e.g. lymphoma, Hypersensitivity
- **Relative:** Active infection, live-attenuated vaccines, other immunosuppressant drugs

Biologics

"Targeted immune modulators"

Biologics are agents that **interfere with T-cell activation** by **targeting**

1. ***T-cells*** themselves,
2. the ***co-stimulatory molecules*** during T-cell / APC interaction or
3. the ***cytokines*** produced by T-cells.

Target	Biologics	Notes
CD2 (on T cells)	**Alefacept**	Prevent interaction with ***LFA-3*** (on APCs)
CD11a (a component of **LFA-1** on T cells)	**Efalizumab**(withdrawn from market, 2009)	Prevent interaction with ***ICAM-1*** (on APCs)
TNF-α	***TNF-α inhibitors*** **(etanercept, infliximab, adalimumab)**	
IL-12 and **IL-23**	**Ustekinumab**	**IL-12** → development of **Th1** **IL-23** → development of **Th17**
IL-17 A	**Secukinumab, ixekizumab**	
IL-17RA "receptor"	**Brodalumab**	

Side effects:

1. Increased risk of **infections** or **reactivation of latent infections** e.g. **tuberculosis**, bacterial sepsis, systemic fungal infections (e.g. histoplasmosis), hepatitis B virus reactivation and infections due to opportunistic pathogens (this is particularly important for **TNF-α inhibitors**).
   Anti-TNF-α (infliximab & etanercept): Increase incidence of infection of **TB infection** (latent TB focus → active lesion) مهم جداً

2. Could potentially increase the risk of **malignancies** (especially **lymphomas**).

3. **Hypersensitivity** reactions (e.g. urticaria, angioedema up to anaphylaxis).

4. **Cardiovascular** and **CNS** complications.

Investigations (base-line):

- CBC
- Screening for infection:
  - TB: CXR – tuberculin test - PPD – Interferon-γ release assay
  - Liver: hepatitis markers
  - HIV / AIDS
- Kidney / liver function tests

Follow-up:

1. Clinical: any signs of infection (fever, sore throat….)
2. Lab: CBC
3. Measures to prevent infection: **vaccines**
   - **Killed vaccines: YES**
   - **Live-attenuated vaccines: NO (contraindicated)**

Contraindications:

ANY active **infection**

Photo(chemo)therapy

Definition:

- ***Phototherapy*** is the use of ultraviolet radiation (**UVR**) for the treatment of skin diseases.
- ***Photochemotherapy*** means the combination of a **photosensitizer** (e.g. **psoralens**) with UVR.

Electromagnetic spectrum:

Ultraviolet (UV)	Visible	Infra-red (IR)
< 400 nm	**400 – 700 nm** 400 violet (shortest) 700 red (longest) ألوان الطيف السبعه	**> 700 nm**

Ultraviolet (UV)				
UVC **200-290 nm** أقصر حاجه	**UVB** **290-320** قصير		**UVA** **320-400** طويل	
Absorbed by the oxygen and ozone in the earth's atmosphere (**Does NOT reach the surface of the earth**) **Carcinogenic** / No phototherapeutic potentials Used as **germicidal**	**Broadband (BB-UVB)** **290-320** كله	**Narrowband (NB-UVB)** **311-311 nm** أطول شويه	**UVA2** **320-340**	**UVA1** **340-400** أطول حاجه Treatment of **scleroderma**

NOTES:

- **100-200 nm: vacuum UV (industry)**
- **<100 nm = ionizing radiation e.g.** X-ray, Gamma ray (carcinogenic, used in radiology and radiotherapy)
- **Advantages of NB-UVB over BB-UVB:**
  - More therapeutic effect and less side effects (erythema)
  - Disadvantage: more expensive
- **Rule: the longer the wavelength, the deeper the penetration** مهم جدا

Effects of UV radiation on skin:

***Acute** (EARLY) effects:*

(1) Sunburn (Erythema)

- Mainly due to **UVB** radiation
- **UVA** may also cause sunburn but requires approximately **1000-fold higher** doses than UVB

(2) Tanning

(3) Epidermal hyperplasia

(4) Vitamin D synthesis (UVB: 7-dehydrocholesterol → vitamin D2)

(Rickets الأطفال – التعرض للشمس - النوافذ)

(5) Photoimmunosuppression: مهم جدا

- Depletion of LCs → ↓ antigen presnetaion
- Alteration of Th1 / Th2 cytokines media
- Inhibition of delayed type hypersensitivity
- Inhibition of contact type hypersensitivity

(6) Photosensitivity disorders e.g. polymorphus light eruption (PMLE)

(7) Disturbance of skin barrier function: ↓ lipid and ↑ water loss (dryness)

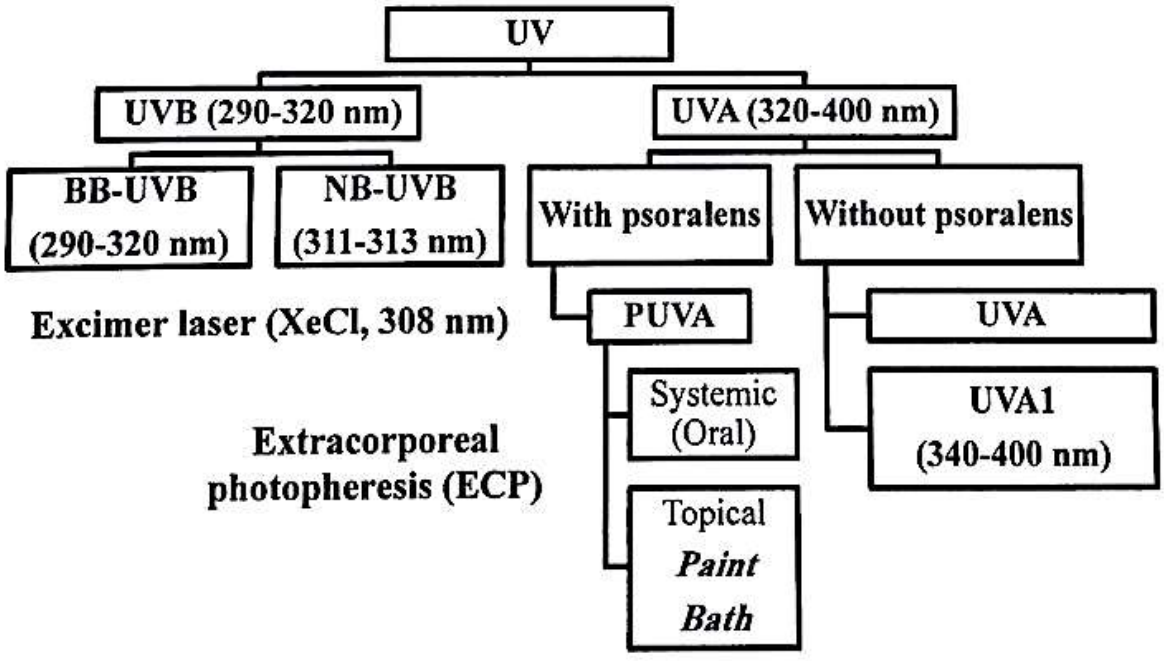
***Chronic** (LATE) effects:*

1. Photoaging = extrinsic aging
2. Carcinogenesis = NMSC (BCC, SCC) + Melanoma

Effects of UVR: أهمية

Mechanism of therapy, side effects, contraindications

Phototherapeutic modalities:



Phototherapy = UVR ± psoralens

Actions / Mechanisms of actions:

- **Anti-proliferative:** inhibits keratinocyte proliferation.
  - **UVB (BB, NB, Excimer), UVA:** direct effect
  - Psoralens (photosensitizer), in the presence of UVA, interacts with DNA double helix → mono- and bi-adduct → inhibit DNA replication and synthesis → ↓↓ epidermal cell proliferation
- **Immunomodulatory:**
  - Depletion of LCs → ↓ antigen presnetaion
  - Alteration of Th1 / Th2 cytokines media
  - ~~Inhibition of delayed type hypersensitivity~~
  - ~~Inhibition of contact type hypersensitivity~~
- **In vitiligo:**
  - Stimulates migration of melanocytes from surrounding normal skin and hair follicles.

Indications: *Immune suppression / modulation + Anti-proliferative*

Common indications:

- **Psoriasis.**
  - **Moderate-to-severe** psoriasis **not responding to topical** therapies – may be used alone (**monotherapy**) or in **combination** (with topical / systemic agents).
- Vitiligo.
- Mycosis fungoides (stages IA, IB, IIA).
- Atopic dermatitis.
- Prurigo nodularis.
- Pruritus.
- Generalized lichen planus.

Less common indications:

- Pityriasis lichenoides (acute and chronic).
- Pityriasis rubra pilaris.
- Pityriasis rosea.
- Cutaneous graft versus host disease (GVHD).
- **Photosensitivity disorders:** *** **Desensitization** (very small dose of UVR then gradually increased = **hardening**)
  - Polymorphic light eruption (PMLE), Solar urticaria, Chronic actinic dermatitis, Hydroa vacciniforme, Erythropoietic protoporphyria.

- Localized scleroderma / morphoea (UVA1).
- Alopecia areata.
- Seborrhoeic dermatitis.
- Urticaria pigmentosa.
- Generalized granuloma annulare.
- Lymphomatoid papulosis.
- Purpura pigmentosa chronica.
- Dyshidrotic eczema.
- Langerhans cell histiocytosis.

Contraindications:

- Active viral infections e.g. herpes flare (relative contraindication)
- Immunosuppression

- Inherited defective repair of UV-induced damage in DNA e.g. Xeroderma pigmentosum
- Albinism (high risk of developing skin cancer)
- History / Past history of melanoma / non-melanoma skin cancer, previous treatment with ionizing radiation or arsenic, and extensive solar damage

- Photosensitivity **EXCEPT** ???
- Disorders induced / aggravated by UVR e.g. Lupus erythematosus (with a photosensitivity or a positive Ro antibody test)

- **Psoralens:** Uremia and severe hepatic failure (drug metabolism and excretion) will be disturbed

Pregnancy / Lactation:

- Contraindication for PUVA therapy
- **UVB (NBUVB) phototherapy may be used (TR of choice in pregnancy) **** مهم جدا**

Side effects:

- **Acute:** erythema, burn, tanning, skin dryness (pruritus), reactivation of latent viral infections and photosensitivity.
- **Chronic:** photoaging (wrinkles + **PUVA lentigens**) and increased risk of cutaneous cancer (NMSC: SCC, BCC).
- **Side effects of psoralens: Nausea, vomiting (مهم جدا),** Hepatotoxicity, increased risk of **cataract** (PUVA).

Dosing (Dosimetry):

Dose of psoralen (PUVA)

- 8-methoxypsoralen (8-MOP)
- Neomedanin 10 mg tab, Oxsoralen 10 mg cap
- 0.6 – 0.8 mg/kg, 1.5 – 2 hours before session
- On empty stomach (food ↓ absorption) BUT nausea and vomiting (light food e.g. milk or jam – same time every session)

UVR: 3 items

1. Starting dose
2. Frequency of treatment
3. Increment regimen

(1) Starting dose

- **Skin phototype (I – VI): American protocol "less aggressive"**

NB-UVB

According to skin type:

Skin type	Initial UVB dose, mJ/cm²	UVB increase after each treatment, mJ/cm²	Maximum dose, mJ/cm²
I	130	15	2000
II	220	25	2000
III	260	40	3000
IV	330	45	3000
V	350	60	5000
VI	400	65	5000

PUVA

Table VIII. Dosing of ultraviolet A radiation for oral psoralen plus ultraviolet A

Skin type	Initial dose, J/cm²	Increments, J/cm²	Maximum dose, J/cm²
I	0.5	0.5	8
II	1.0	0.5	8
III	1.5	1.0	12
IV	2.0	1.0	12
V	2.5	1.5	20
VI	3.0	1.5	20

- **According to MED / MPD: European protocol "more aggressive"**
  - 50% , 70% or 100 % MED/MPD

MED

- ***Definition:*** the lowest dose that causes a minimally perceptible erythema reaction at **24 hours** after irradiation **(UVB)**
- ***How to calculate:*** lower back → covered with a template cut out of cardboard with 6 – 8 small squares (3 x 3 cm) → expose to an increasing range of doses of UVB radiation (e.g. 0.5, 1, 1.5, 2…) and then examine the response **24 hr later**
- ***Another rapid method:*** a **template (hand-held)** is applied to the skin with **apertures** containing variably **perforated metal grills** that differentially attenuate the radiation. A **single exposure** from a fluorescent lamp mounted closely above the template then results in a graded series of doses **(rapid)**

MPD

- Ingest **psoralen** (in usual dose), expose to **UVA**, read after **72 hrs**

MED	UVB	24 hrs	No drug intake
MPD	UVA	72 hrs	Psoralen ingestion

(2) Increment regimens

- 10 %
- 20 %
- 30 %
- 40 %
- Fixed increment

(3) Frequency:

- **2 / week**
- **3 / week**
- 4 / week
- 5 / week

Baseline monitoring:

- **Liver / kidney function tests and eye examination (PUVA)**
- ANA / anti-Ro (if indicated)
- Screening for cancer (if indicated)

Precautions:

- **During session: covering genitalia + goggles**
- In case of PUVA, wear goggles for the whole day of the session (24 hrs): T ½ of psoralens = 2 hrs

NOTES:

- **Effect on eye:**
  - **UVB: cornea**
  - **UVA: lens** (longer wavelength and deeper penetration)
- **Choice of therapy (in psoriasis)**
  - **UVB:** short wave, epidermis + superficial dermis (thin lesions e.g. guttate) + safe (pregnancy, lactation, children)
  - **UVA:** long wave, epidermis + dermis (thick lesions e.g. PP, nail, thick plaque)
- **Combination phototherapy:**

Topical:

- **Ingram** regimen (a **combination** of dithranol with UV light).
- **Goeckerman** regimen (a **combination** of crude coal tar with UV light)
- Topical **salicylic acid** decreases the efficacy of UVB phototherapy (a filtering effect). It therefore should **not** be **applied before** UVB phototherapy
- **Calcipotriene** is **inactivated** by UVA. So, it is important to apply calcipotriene **after** and **not before** UVA exposure

Systemic: MTX, retinoids + PUVA = Re-PUVA

Sunscreens

Definition

Pharmaceutical preparations that attenuate UV radiation and minimize its harmful effects on the skin

Composition 2 compnents:

1. **active agents / ingredients:** attenuate UV radiation
2. **base:** in which active agents are dispersed

NB. active ingredients are ***not absorbed*** in any large quantity into the living epidermis or dermis or the general circulation

Sunscreen efficacy

sunscreens protect against **adverse effects of sun exposure**

1. sunburn
2. photoaging
3. carcinogenesis (non-melanoma skin cancer, SCC+BCC)
4. photoimmune suppression
5. photosensitivity

Effect	Spectrum of light		
	UVB 290-320 nm	UVA 320-400 nm	Visible 400-700 nm
Sunburn	++++	+	
Photoaging	++++	++	?
Squamous cell carcinoma	++++	+	
Basal cell carcinoma	+++	?	
Cutaneous melanoma	++	+	
Photoimmune suppression	++++	++	
Photosensitivity	+	+++	+

NB 2. UVA (320-400 nm):

UVA2 (320-340 nm) – UVA1 (340-400 nm)

NOTE: most adverse effects (sunburn, photoaging, NMSC and photoimmune suppression) **EXCEPT photosensitivity**: produced by UVB > UVA e.g **UVB is 1000 times > UVA at inducing erythema radiation**
BUT UVA also plays a greater or lesser role

- photoaging was originally thought to be primarily due to UVB (UVA penetrates more deeply)
- sunscreens with only UVB protective agents are not totally effective in blocking photoimmune suppression
- there is 10 to 20 times as much UVA as UVB in sunlight. This ratio is even higher for individuals using UVB-protective sunscreen → stay in the sun longer and get larger amounts of UVA radiation

so, it is better to use **broad-spectrum sunscreens (UVB/UVA)**

Sun Protection Factor (SPF)

measure of efficacy of sunscreens
SPF = MED in protected skin / MED in unprotected skin
MED = minimal erythema dose

SPF	Blockage of *erythemal* radiation (%)
10	90
15	92.5
20	95
40	97.5

- **NB 1.** SPF 20 product does not absorb twice as much radiation as SPF 10 product
- **NB 2.** SPF is a measure for protection against erythema/burn (UVB 1000 times > UVA)
- **NB 3. FDA (August 2007):** SPF renamed as ***sunburn*** protection factor
- **NB 4. testing for protection against long-wave UVA:**

?? why not erythema ??

in vivo → tanning response to UVA radiation:

1. ***immediate pigment darkening*** (darkening of pre-formed melanin)
2. ***delayed (persistent) pigment darkening*** (increased production and transfer of melanin + proliferation of melanocytes)

FDA (August 2007)

in vitro → **critical wavelength** determination: wavelength at which 90% of solar-simulated radiation above 320 nm is absorbed

Types and mechanism of action:

Sunscreens applied onto the skin form a film/coating on stratum corneum, attenuate radiation by **absorbing or scattering** and prevents it from reaching the living epidermis and dermis

Physical agents (sunblockers)	Chemical agents (sunscreens)
inorganic materials	Organic compounds
Scatter radiation → reflected back out of the skin	absorb radiation → energy absorbed is converted to non-damaging energy and dissipated as heat
scattering depends on particle size (NB 3)	absorption depends on chemical structure
opaque particles	
e.g. titanium dioxide and zinc oxide	e.g. Para-aminobenzoic acid (PABA) and its derivatives – Salicylates
Protect against UVB, UVA2, UVA1 ± visible	Most of them protect against UVB ONLY Only few protects against UVA2, UVA1

- **NB 1:** many sunscreen products today contain combinations of both types & two or more agents to offer high levels of protection
- **NB 2:** ***'chemical-free' products:*** contain only inorganics
- **NB 3:**

	Physical gents with *large* particle size	**Agents with *small* particle size (micronized)**
Advantages	good protection (UVB, UVA2, UVA1) ± visible	more cosmetically acceptable
Disadvantages	opaque appearance → not acceptable cosmetically	Less protective: shifting protection toward UVA2 (actually act like organic sunscreens scattering and absorbing)

Adverse effects: Sunscreens are generally safe

- minor skin irritation (common)
- allergic contact dermatitis (rare)
    - due to ingredients in the base of the product (fragrance or preservatives)
- ??? blocking the production of vitamin D (→ ↓ musculoskeletal health, ↑ risk of cancer , ↓ immune function)
    - sunscreens that block UVB photons decrease levels of vitamin D (<u>BUT</u> within the normal range)
    - recommendation: all individuals should maintain adequate vitamin D intake through diet and supplements
- ??? mutagenic / carcinogenic / adverse hormonal effects (in vitro and animal studies)

Photodynamic therapy (PDT)

Definition

Use of cytotoxic oxygen radicals (mainly singlet oxygen, $^1O_2$) generated from photoactivated molecular species to achieve a therapeutic response.

Components

1. Photoactivating light
2. Exogenous photosensitizer
3. Tissue oxygen
4. Target cell

Mechanism of action

- Interaction between photoactivating light, photosensitizer and tissue oxygen creates **singlet oxygen ($^1O_2$)** → very potent oxidant species → oxidize cellular components (lipid, peptides, nucleic acids) → **oxidative damage** & cell death.
- A **time period** is required after drug administration to allow photosensitizer production and accumulation into targeted tissue/cells e.g. **24 h (topical ALA)**, 2–4 h (oral ALA)

Target cells undergo either:

1. **apoptosis** due to ***membrane-bound*** photosensitizers
2. **ischemic necrosis** due to ***vascular injury*** from photosensitizers concentrated in endothelial cells
3. **both**

Photosensitizers

- **Topical**
  - 5-(δ-)aminolevulinic acid (ALA) (Levulan®)
  - Methyl-esterified ALA (mALA) (Metvix®)
- **Systemic**
  Oral 5-(δ-)aminolevulinic acid (ALA) (Levulan®)
  Intra-venous e.g. Porfimer Na (Photofrin®)

NB 1. Only ALA and mALA are FDA-approved **only for AK**

NB 2. ALA and mALA are ***precursors*** of photosensitizers – they are converted in vivo into protoporphyrin IX (PpIX)

Photoactivating light sources

Requirements of a good light source

- low-power (low-irradiance): does not create photothermal or photomechanical effects
- light source's spectral output must match absorption peak of the photosensitizer
- wavelength must be longer than that of UV spectrum (i.e. >400 nm): risk of cancer
- must have sufficient photon energy to initiate photochemical processes (<800 nm)
    - **therapeutic wavelength window for PDT: 400 – 800 nm**
        - **epidermal lesions: blue light**
        - **dermal lesions: red light (deeply penetrating)**

Types of light sources used:

- laser light sources:
    - argon-pumped tunable dye laser (630 nm)
    - diode lasers
- light-emitting diodes (LED)
- filtered broadband lamp sources

Indications

Oncologic:

- Basal Cell Carcinoma (most common oncologic indication)
- Squamous Cell Carcinoma *in situ* (including erythroplasia of Queyrat – Bowen's disease)
- Paget's disease
- Actinic Keratoses
- Actinic Cheilitis
- Mycosis Fungoides / Cutaneous T-Cell Lymphoma
- Melanoma
- Kaposi's sarcoma (KS)

Non-oncologic:

- Capillary vascular malformations:
    - Port-Wine Stains
- Inflammatory:
    - Psoriasis
    - Acne
- Infections:
    - Human papillomavirus infections: Verrucae and condylomata
    - cutaneous leishmaniasis
- Photodamage

Adverse effects and complications:

vary with photosensitizer / light source used

- **Pain:** the most common side effect
- **Cutaneous photosensitivity and photophobia**
- **Treatment site reactions:** edema – crusting – occasional blistering followed by slough and healing – pruritus – hypopigmentation ± scarring (at site of healed ulcers) – hypertrophic scar – permanent alopecia
- **Allergic Contact Dermatitis:** topical ALA

- **Constitutional Symptoms:** nausea, vomiting, headache and flu-like symptoms
- **Liver toxicity:** dose-dependent elevation of hepatic enzyme and bilirubin levels (photosensitizers undergo hepatic metabolism)
- **Mutagenic Potential: ??**
    - ?? PDT-induced oxygen free radicals
    - ?? Immunosuppression

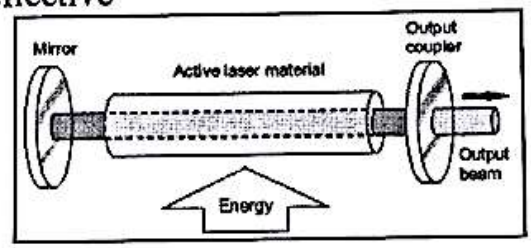
Laser

Definition: Laser is an **acronym** for **"Light Amplification by Stimulated Emission of Radiation"**

Principle of action: Stimulated emission of radiation

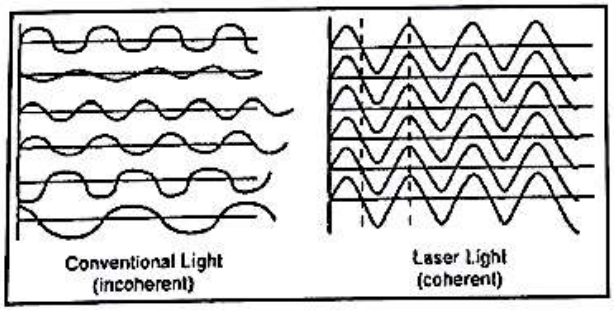
Components of laser apparatus

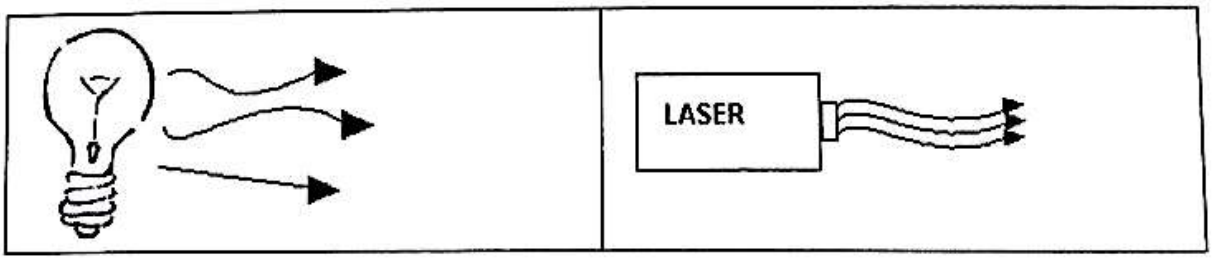
1. Active medium
2. Source of pumping energy
3. 2 mirrors:
   - Totally reflective
   - Partially reflective



Properties of laser light:

1. **Monochromatic:** single wavelength
2. **Coherent:** highly ordered pattern "in phase"
3. **Collimated:** parallel with a minimal degree of divergence
4. **High power**





Types of lasers:

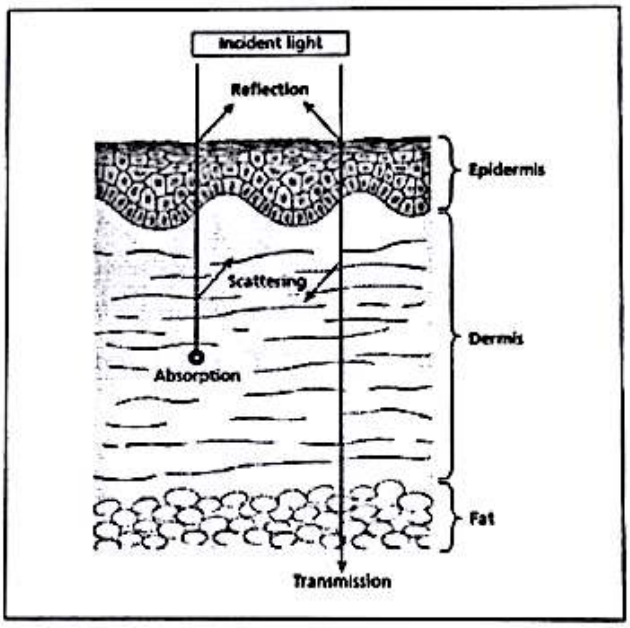
- *According to active medium:*
  - **Solid-state lasers:** KTP (532 nm) – ruby (694 nm) – Alexandrite (755 nm) – Nd:YAG (1064 nm) – Er:YAG (2940 nm)
  - **Liquid:** pulsed dye lasers (585 – 595 nm)
  - **Gas:** CO_2 (10600 nm) – excimer XeCl (308 nm)
  - **Semiconductor:** diode laser

- *According to pumping source:*
  - Electric discharge
  - Optical pumping
  - Chemical reaction
  - Another laser

- *According to emission spectrum:*
  - **Ultraviolet:** excimer
  - **Visible:** ruby – dye
  - **IR:** CO_2 – Nd:YAG – Er:YAG

- *According to mode:*
  - **Continuous wave (CW)**
  - **Pulsed:**
    - ☑ **long-pulse (ms)**
    - ☑ **Q-switched (ns)**

- *According to power:*
  - **High power:** CO2
  - **Low power:** diode – He-Ne



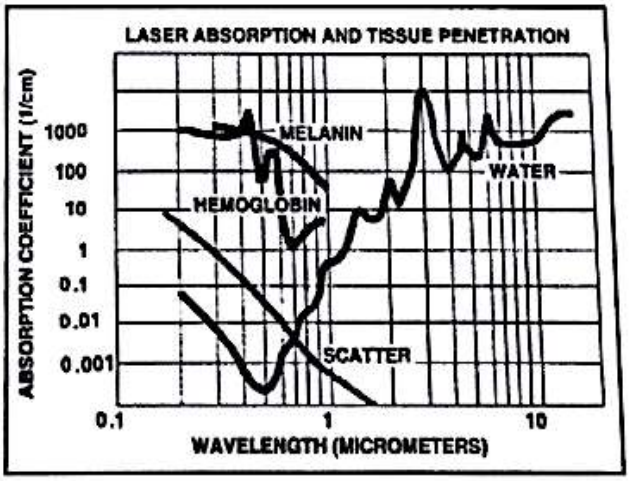
Laser-tissue interactions:

- Laser light interacts with the skin in 4 principal ways:
  1. Reflection
  2. Scattering
  3. Transmission
  4. Absorption
- Tissue effects occur **only** when light is **absorbed**
- Reflection, Scattering and Transmission: concerned with laser safety

- When absorption occurs, the laser light transmits its energy to the chromophore leading to:
  1. **Photothermal effect:** coagulation / vaporization of tissue
  2. **Photomechanical (photo-acoustic) effect:** tissue disruption by pulsed lasers (pigmented lesions)
  3. **Photochemical effect:** breakage of chemical bonds or chemical interaction (PDT)
  4. **Photobiostimulation effect:** tissue stimulation with very low level laser (LLL)

Mechanism of action of lasers in dermatology: "Selective photothermolysis"

- Selective destruction of certain targets in the skin and sparing surrounding structures
- These targets are called "chromophores"
- Each chromophore selectively absorbs light of certain wavelengths "*absorption spectrum*"
- Selective destruction of certain target necessitate adjustment of 3 laser parameters:
  1. Wavelength
  2. Energy / Power
  3. Pulse duration (in pulsed lasers)
- Important chromphores in skin include:
  1. ***Hemoglobin***
  2. ***Melanin***
  3. ***Water***



Chromophore	Absorption spectrum	Applications	Lasers used
Hemoglobin	Visible Near IR	Vascular lesions	**PDL** – KTP – Alexandrite – Diode – Nd:YAG
Melanin	UV Visible Near IR	Pigmented lesions and tattos	**Ruby** – KTP – Alexandrite – Diode – Nd:YAG ***(Q-switched = ns)*** لازم
		Hair reduction	Ruby –Alexandrite – Diode – Nd:YAG ***(Long-pulsed = ms)*** لازم
Water	Mid-Far IR	Skin resurfacing (rejuvenation)	CO_2 – Er:YAG
		Vaporization of epidermal lesions (warts...)	

Indications

(A) Therapeutic

- **Vascular lesions:** PWS – hemangiomas – telangiectasia – varicose veins
- **Pigmented lesions:** (epidermal / dermal / mixed) Lentigens – freckles – melasma – nevi (melanocytic / Ota..)
- **Tattoo removal:** decorative / cosmetic / medical / traumatic
- **Hair reduction:** hirsutism – hypertrichosis – …
- **Skin resurfacing (rejuvenation):** photodamaged skin (wrinkles) – scars
    - *Ablative:* CO_2 – Er:YAG
    - *Non-ablative:* PDL – KTP – Diode
- **Vaporization of surface epidermal lesions:** warts – SK – AK … (Ablative lasers)
- **Laser-mediated photodynamic therapy**
- **Other indications:**
    - Psoriasis – vitiligo (XeCl excime 308 nm مهم)
    - Hypertrophic scars – keloids – striae distensae (PDL)
- **Photobiostimulation:** wound healing & pain relief (low-power lasers)

(B) Diagnostic

- IR-laser confocal microscopy: epidermis and upper dermis can be examined rapidly *in vivo* e.g. skin tumors
- Optical coherence tomography (OCT)

Side effects / complications:

- Pain / Eythema / Edema
- Post-inflammatory hyper- or hypo-pigmentation (**MOST COMMON**)
- Scarring / Keloid formation
- Milia / acneform eruption / infection (bacterial, viral): in Ablative Skin Resurfacing

Laser hazards and safety

	Hazards	Safety precautions
Beam hazards	• Fire • Skin: thermal burns • Eye: ocular damage (retina)	• Avoid alcohol – wet drapes • Protective clothings • Protective googles
Non-beam hazards	Plume (human papilloma virus - CO_2 laser vapor)?? Infectivity	Smoke evacuators
		OTHERS: "DANGER" labels Door opens – laser stops

Antimalarials

Chemistry: Antimalarials include:

1. **Quinine (the parent compound):**
   - derived from the ***bark*** of the ***cinchona tree*** in ***South America***
   - was first used in dermatology by Payne in 1894 to treat ***discoid*** lesions in patients with lupus erythematosus (***LE***)

Synthetic Antimalarials (SAMs)

2. **Hydroxychloroquine (HCQ)** (Plaquenil®)
3. **Chloroquine (CQ)** (Aralen®)
4. **Quinacrine (US) / (Mepacrine in UK)**
   - can lead to ***yellow discoloration of the skin***
   - ***only*** available via ***compounding pharmacies in the US***

Actions / Mechanism of Action: **not well known**. These drugs:

1. exert various **anti-inflammatory** effects: Inhibit a number of inflammatory pathways, including secretion of macrophage and monocyte-derived cytokines and Toll-like receptor signalling in response to DNA associated autoantigens

2. **inhibit antigen presentation to T cells:** they are highly **concentrated** within **intracellular lysosomes** where they **inhibit acidic proteases**. This may be particularly important in **antigen-presenting cells** where they **interfere with** the **digestion** and subsequent **presentation** of **antigens** to **T cells.**

3. can **inhibit** interleukin-2 **(IL-2)** release from **T-helper** (CD4+) cells
4. may **inhibit macrophage expression** of **MHC antigens**
5. **decrease platelet aggregation**

6. **may affect UV absorption in the skin:** the photoprotective nature of SAM is not entirely understood, but seems related to their ability to ***bind to DNA and RNA*** rather than to a direct sunscreening effect. The triplet state of DNA can transfer energy to the triplet state of CQ, thereby interfering with UV-induced thymine dimer formation. CQ may be intercalated between base pairs, serving as a kind of ***photon sink***.

Indications:

Cutaneous LE: the ***most common dermatologic use*** of antimalarials

- ***second-line therapy***, after topical or intralesional corticosteroids
- especially useful in patients with ***widespread discoid lesions*** and in those with the annular or papulosquamous lesions of ***subacute cutaneous LE (SCLE)***.

Other diseases that may respond to antimalarial therapy include:

1. lupus panniculitis
2. the cutaneous manifestations of Dermatomyositis
3. Photodermatoses (especially polymorphous light eruption - solar urticaria)
4. porphyria cutanea tarda
5. Cutaneous Sarcoidosis
6. granuloma annulare
7. (oral) lichen planus
8. chronic GVHD
9. lymphocytic dermal infiltrates (including LE tumidus)
10. reticular erythematous mucinosis

Dosages:

	Hydroxychloroquine	Chloroquine
Most conditions will respond to	200 – 400 mg / day	250 mg / day
Maximum safe dose (from an ocular standpoint)	6.5 mg/kg/day	4.0 mg/kg/day (3 ROOK)

Side Effects:

(1) Ophthalmologic أول هام:

- reversible (early) and irreversible ***retinopathy, vision changes*** ***Rare***
- the ***risk of retinopathy*** is ***much less with hydroxychloroquine*** as compared with chloroquine.
- ***Retinopathy*** risk is greatest for:
  - those on treatment for ***at least 5 years*** (especially with ***chloroquine***)
  - if ***maximum daily safe dose*** has been exceeded (dose-related ocular toxicity)
- **Mepacrine (Quinacrine) lacks ocular toxicity**

(2) Hematologic تانى هام:

- **Hemolysis (G6PD-deficient)**
- Pancytopenia (Agranulocytosis and aplastic anaemia)

Haemolytic anaemia may be precipitated in patients with glucose-6-phosphatase deficiency. This possibility should be considered before starting therapy in patients from ***populations where this deficiency is prevalent.*** السعودية

(3) Dermatologic:

- blue–gray to black ***discoloration*** **(yellowing from quinacrine)**
- Antimalarials have been reported to ***worsen psoriasis*** in some patients
- *reversible* bleaching of hair roots (***achromotrichia***)
- exanthema (skin rash)

(4) Gastrointestinal: nausea, vomiting, elevated liver enzymes
(5) Neurological: irritability, nervousness

Monitoring guidelines:

Initial screening:

Ocular:

Because of the risk of ***dose-related ocular toxicity***, a ***referral to an ophthalmologist*** is necessary for examination at ***baseline*** and then ***every 6 to 12 months***

- assessment of ***visual acuity***
- ***visual field*** testing
- ***slit lamp*** examination
- ***fundoscopic*** examination

Laboratory:

- ***CBC***
- comprehensive metabolic panel (CMB) including ***liver function tests***
- ***G6PD*** (selected cases): G6PD testing before antimalarial therapy is ***controversial***
- ***Urine or serum porphyrins*** should be measured when ***porphyria*** is clinically suspected

Follow-up monitoring:

- ***Ocular:*** repeat testing every 6 months for 1 year and then yearly
- ***CBC:*** monthly for 3 months, then every 4–6 months
- ***CMP:*** after 1 and 3 months, then every 4–6 months

Contraindications:

The only true contraindication is ***hypersensitivity*** to the drug.

Caution should be used in patients with:

- ***severe blood dyscrasias*** or ***hepatic disorders***
- ***Ophthalmologic changes***

Over-dosage (Toxicity):

An overdose of antimalarials can be ***fatal***, and although pediatric usage is safe and effective, patients should be warned to keep the drug out of the reach of small children.

Use in Pregnancy and Lactation:

- ***Chloroquine*** → reports of an increase in ***birth defects*** in pregnant women being treated for systemic LE (***SLE***).
- ***Hydroxychloroquine*** is thought to be ***safer*** during pregnancy, even with its much longer half-life.
- Although ***excreted into breast milk***, standard doses of either drug are ***not harmful to breastfed infants*** and are *approved by the American Academy of Pediatrics for use during lactation.*

Drug Interactions:

↑ circulating levels of antimalarials	Cimetidine
antimalarials ↑ levels of	Digoxin
↓ absorption of antimalarials	Kaolin – magnesium trisilicate – over-the-counter gastrointestinal drugs

The ***most significant*** potential interaction is the **additive risk of retinal toxicity** when **chloroquine and hydroxychloroquine** are used concomitantly. Combined therapy consisting of chloroquine or hydroxychloroquine plus quinacrine is acceptable.

مهم – التدخين In patients with **LE, cigarette smoking** has been associated with **decreased efficacy** of antimalarials. Whether this represents a 'drug–drug' interaction or decreased compliance (as a manifestation of high-risk behavior) is not known.

Dapsone

- **Chemistry:** 4',4' diamino-diphenyl sulfone

- **Mechanism of Action**
  - Dapsone inhibits **neutrophil** chemotaxis / myeloperoxidase and **IgA** adherence.

- **INDICATIONS:**

Dapsone is clinically most useful in the treatment of dermatologic **diseases involving neutrophilic infiltrates.**

- **Leprosy**
- **FDA-approved: DH**
- **AI-bullous with neutrophils:**
  - **IgA pemphigus**
  - **LABD / bullous SLE / DH**
- **Neutrophilic dermatoses: Behcet's, PG, Sweet's, EED**
- Immunosuppressant (2nd line after steroids):
  - Vasculitis (CSVV)
  - Other AI-bullous

- **Dose:**
  - Initial dosages: 25-50 mg in adults / 0.5 mg/kg in children
  - Initiation of therapy with **higher doses** may precipitate ***severe hemolysis*** and ***cardiac decompensation*** in susceptible individuals
  - average maintenance dose in adults 100 mg daily

Side effects:

1. **Haematological**
   - ***Red blood cell toxicity***
     - Hemolytic anemia
     - Methemoglobinemia
   - ***White blood cell toxicity***
     - Leukopenia
     - Agranulocytosis
2. **Dapsone hypersensitivity syndrome:**

Hepatitis, lymphadenopathy, fatigue, anorexia

3. **Cutaneous reactions**
   - Morbilliform eruption
   - Urticaria
   - Fixed drug eruption
   - Erythema nodosum
   - Exfoliative dermatitis
   - Stevens-Johnson syndrome
   - Toxic epidermal necrolysis
   - Phototoxicity
   - Drug-induced lupus erythematosus
4. **Gastrointestinal manifestations**
   - Anorexia, nausea
   - Hepatitis
   - Cholestatic jaundice
   - Severe hypoalbuminemia
5. **Neurologic associations**
   - Headache, dizziness
   - Peripheral neuropathy
   - Blurred vision, tinnitus
   - Insomnia
   - Psychosis
6. **Miscellaneous**
   - Fever
   - Nephrotic syndrome

Hemolysis:

- occurs in virtually ***every patient*** on dapsone therapy, since sulfones produce an ***oxidant stress*** for ***aging red blood cells***
- In patients with ***glucose-6-phosphate dehydrogenase deficiency***, dapsone may produce ***severe hemolysis***

Methemoglobin:

- Methemoglobinemia in the absence of cardiopulmonary symptoms does not require alteration of dapsone dose

If patients are **intolerant to dapsone**, therapy with **sulfapyridine** should be considered. The initial dose of sulfapyridine is usually 500 mg three times a day and it can be safely increased to 2 g three times a day; however, some patients may not respond to sulfapyridine at any dose. Adequate fluid intake and alkalinization of the urine minimizes the risk of **nephrolithiasis**

Dapsone therapy requires **baseline investigations**

1. **complete blood count (CBC)**
   - weekly CBCs for the first month
   - monthly CBCs for the next 5 months
   - semiannual CBCs thereafter *while the patient remains on therapy*
2. **Liver function tests**
   - should be repeated at 6 months and annually thereafter
3. **glucose-6-phosphate dehydrogenase activity**
   - ➢ should be assessed in African-Americans, Asians, and those of southern Mediterranean ancestry

Sulfapyridine does not produce hemolytic anemia, but the potential for agranulocytosis does exist. Consequently, similar monitoring is recommended for chronic sulfapyridine therapy.

Topical corticosteroids

Classes:

- 3 Factors:
  - Concentration
  - Vehicle i.e. cream, oint, lotion, gel…
  - Acid e.g. propionate, dipropionate, valerate…
- 2 systems:
  - American 7
  - British 4

CLASS 1 (SUPERPOTENT)
- Clobetasol propionate 0.05% (Dermovate) gel, ointment, cream, lotion, foam, spray and shampoo
- Betamethasone dipropionate 0.05% (Diprosone) gel and ointment

CLASS 2 (HIGH POTENCY)
- Betamethasone dipropionate 0.05% (Diprosone) cream, lotion, **gel and ointment** 0.05%
- Clobetasol propionate 0.05% (Dermovate) solution ("scalp application")

CLASS 3 (HIGH POTENCY)
- Betamethasone valerate 0.1% (Betnovate) ointment
- Fluticasone propionate 0.005% (Cutivate) ointment

CLASS 4 (MEDIUM POTENCY)
- Mometasone furoate 0.1% (Elocon) cream and lotion
- Triamcinolone acetonide 0.1% (Topicort) ointment and cream

CLASS 5 (MEDIUM POTENCY)
- Prednicarbate 0.1 % (Dermatop) ointment and cream 0.1%

CLASS 6 (LOW POTENCY)
- Alclometasone dipropionate 0.05% (Perderm) ointment and cream

CLASS 7 (LOW POTENCY)
- Hydrocortisone

British (4 classes): ***very potent (1), potent (2,3), moderate (4,5), mild (6,7)***

Actions and Mechanisms of actions

The topical corticosteroid …

- diffuses into the target cell
- binds to the glucocorticoid receptor "GCR" in the **cytoplasm**
- the corticosteroid-GCR complex → conformational changes → traverses the **nuclear** envelope → directly or indirectly binds to DNA → gene regulation and transcription of various specific messenger ribonucleic acid (mRNA)

Topical corticosteroids have **3 main actions:**

1. **Anti-inflammatory effects e.g.**
   - Stabilize cell and lysosomal membranes > prevent release of lysosomal contents
   - Inhibit phospholipase A2 and block release of arachidonic acid from cell membranes > prevent formation of potent inflammatory mediators e.g. PGs,TXs, LTs..
2. **Immune-suppressive effects**
   - Reduce number and activity of lymphocytes and monocytes
   - Reduce activation of Langerhans cells
   - Reduce secrtion of inflammatory cytokines
3. **Anti-proliferative and atrophogenic effects**
   - Inhibit keratinocyte mitosis
   - Inhibit fibroblasts > decreased collagen

Indications:

- **Dermatitis (eczema)**
  - Atopic dermatitis
  - Diaper dermatitis
  - Nummular dermatitis
  - Seborrheic dermatitis
  - Dyshidrotic eczema
  - Lichen simplex chronicus
- **Papulosquamous**
  - Lichen planus
  - Pityriasis rosea
  - Psoriasis (?)

- **Bullous dermatoses**
  - Bullous pemphigoid
  - Cicatricial pemphigoid
  - Epidermolysis bullosa acquisita
  - Herpes gestationis (pemphigoid gestationis)
  - Pemphigus foliaceus
- **Connective tissue diseases**
  - Dermatomyositis
  - Lupus
- **Neutrophilic dermatoses**
  - Behçet's disease
  - Pyoderma gangrenosum
- **Other dermatologic uses**
  - Well's syndrome
  - Alopecia areata
  - Acne keloidalis nuchae
  - Chondrodermatitis nodularis helicis
  - Cutaneous T cell lymphoma, patch-stage
  - Granuloma annulare
  - Jessner's lymphocytic infiltrate
  - Lichen planopilaris
  - Lichen sclerosis et atrophicus
  - Morphea
  - Pruritic urticarial papules and plaques of pregnancy
  - Pruritus – perianal, vulvar, scrotal
  - Sarcoidosis
  - Vitiligo

Contraindications:

Absolute

- Known **hypersensitivity** to the topical corticosteroid / a component of the vehicle

Relative

- Bacterial, mycobacterial, fungal, viral **infection**
- Infestation
- Ulceration

Side effects:

Local

- Epidermal atrophy (shiny, wrinkled, fragile skin)
- Telangiectasia & prominent vasculature or purpura
- Striae
- Hypopigmentation
- Facial hypertrichosis
- Steroid addiction/rebound
- Glaucoma/cataracts (around eye)
- Allergic or irritant contact dermatitis
- Tachyphylaxis: tolerance (loss of clinical effect) after repeated doses
- Exacerbation or increased susceptibility to bacterial, fungal, and viral infections
- Steroid-induced rosacea, acne
- Delayed wound healing

Systemic

- Suppression of hypothalamic-pituitary-adrenal axis
- Iatrogenic Cushing's syndrome
- Growth retardation in infants and children

Risk factors for atrophy and other complications:

- Potency
- Amount
- Under-occlusion
- **Location** (face, neck, axilla, groin, and upper inner thighs)
- Lack of physician supervision
- Young age (infancy/childhood)
- Liver / Renal disease "for systemic complications"

Assessment of potency "glucocorticoid assays" e.g.

- Vasoconstrictor assay "human volunteers – volar arm"
- Inhibition of fibroblast growth in vitro "cell cultures"
- Mitotic index suppression "animal studies"

Fingertip unit (FTU):

- the amount of ointment (dispensed from a 5 mm-diameter nozzle) that stretches from the distal crease to the tip of the index finger in an adult.
- One FTU is equal to approximately 0.5 g.
- Approximately 0.5 FTU (0.25 g) is utilized for the area of one side of an extended (flat) hand e.g. palm
- 1 FTU = 2 palms (0.5g)

Intra-lesional corticosteroid therapy

- Triamcinolone acetonide 40 mg/ml (kenacort)
- diluted to the desired concentration = depends on the condition
    - thick dermal lesions such e.g. keloids = 20–40 mg/ml (1:1 or full concentration)
    - AA = 5 mg/ml (1:7)

Systemic corticosteroid therapy (Oral, IM, IV pulse)

According to duration of action

(A) SHORT-ACTING (8-12 hr)

- Hydrocortisone (Solucortef 100 mg/2ml vial)

(B) INTERMEDIATE-ACTING (24-36 hr)

- Prednisone (Hostacortin 5 mg tab)
- Prednisolone (Hostacortin-H 5 mg tab, solupred 5, 20 mg tab)
- Methylprednisolone (solumedrol 0.5 / 1 GRAM amp – urbason 4/8 mg tab)
- Triamcinolone (kenacort 40 mg/ml vial, 4 mg tab)

(C) LONG-ACTING (36-54 hr)

- Dexamethasone (8 mg amp, dexazon 0.5 mg tab)
- Betamethasone (diprofos = B. dipropionate 2 mg, B. NaPhosphate 5 mg)

NB. From A→ C: longer duration, more potency and smaller doses

Mechanism of actions and actions: as topical
Indications: as topical (BUT extensive, severe unresponsive e.g. pemphigus > pemphigoid)

Side effects: مختلف
سكر ضغط قرحه هشاشة عظام
METABOLIC

- **Hyperglycemia******
- **Hyperlipidemia**
- **Obesity**
- Hypocalcemia
- **Hypokalemic alkalosis**

CARDIOVASCULAR

- **Hypertension*******
- Peripheral edema
- Atherosclerosis

GASTROINTESTINAL

- Nausea, vomiting
- Gastroesophageal reflux
- **Peptic ulcer disease******
- Intestinal perforation
- Pancreatitis
- Esophagitis (reflux or candidal)

MUSCULOSKELETAL

- **Osteoporosis*****
- Osteonecrosis (e.g. hip)
- Growth retardation
- Muscle atrophy
- **Myopathy (e.g. in dermatomyositis)**

OPHTHALMOLOGIC

- **Cataracts**
- Glaucoma
- Infection
- Hemorrhage
- Exophthalmos

GYNECOLOGIC, OBSTETRIC

- Amenorrhea
- Fetal effects

HEMATOLOGIC, CELLULAR

- Leukocytosis
- Lymphopenia
- Eosinopenia
- **Immunosuppression**
- Impaired fibroplasia
- Decreased mitotic rate
- **Infections**

NERVOUS SYSTEM

- **Mood, personality changes**
- Psychiatric problems, psychosis
- Seizures
- Pseudotumor cerebri
- Peripheral neuropathy
- Epidural lipomatosis

HYPOTHALAMIC–PITUITARY–ADRENAL (HPA) AXIS

- Suppression
- Withdrawal syndrome
- Adrenal crisis

CUTANEOUS تكتب كامله

Systemic corticosteroid monitoring guidelines

Baseline

Examination

- Blood pressure, weight, height and weight plotted on a growth curve (in children)
- Ophthalmoscopic examination for cataracts

Laboratory

- Fasting glucose
- Fasting triglycerides
- Potassium level
- TB screening (strongly consider) – tuberculin skin test (or IFN-γ-releasing assay), chest X-ray
- CBC

Follow-up:

DEXA scan of hip and lumbar spine (osteoporosis)

Pulse intravenous methylprednisolone therapy = Cardiac monitoring & Daily electrolyte and glucose levels

Supplementation with therapy:

- Calcium
- vitamin D
- potassium
- high protein diet

Contraindications:

- Systemic active / latent infections including latent tuberculosis (unless specific antimicrobial therapy is given).
- Diabetes mellitus.
- Hypertension or congestive heart failure.
- Glaucoma.
- Osteoporosis.
- Active peptic ulcer disease.
- Severe affective disorders/history of corticosteroid induced psychosis.
- Previous steroid myopathy.
- Liver failure.
- Kidney failure.